REMARKS

In response to the Office Action mailed December 19, 2008, Applicants have amended claims 1, 2, 3, 5, and 10. Claims 7 and 8 have been canceled and no new claims have been added. It is urged that support for all the above amendments may be found throughout the specification as originally filed, for example, on pages 6-8. No new matter has been added. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made solely to clarify a particular aspect of the presently claimed invention, without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendments, claims 1-6 and 9-10 are pending and under examination. Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

Claims Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-3, 5, 7, and 9-10 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants respectfully traverse these bases for rejection and submit that the metes and bounds of the present claims are both clear and definite.

The Examiner contends that the term "derivative" is ambiguous since derivative is referring to material "derived" from the named formula. Applicants respectfully disagree. Applicants, without acquiescence, have amended claims 1 and 5 to recite "pharmaceutically acceptable salts, stereoisomers, hydrates, or solvates thereof" in place of the term "derivatives". Support for this amendment can be found throughout the specification as filed, for example, on pages 6-8. Applicants respectfully submit that this basis of rejection has been obviated. Reconsideration and withdrawal of this basis of rejection is respectfully requested.

The Examiner further contends that claims 5, 7, and 10 are of improper form as allegedly being multiple dependent claims depending from another multiple dependent claim. Applicants, without acquiescence, have amended claim 3 to recite "Compounds according to

claim 1~~ or 2~~"; thus, obviating this basis of rejection. Accordingly, Applicants respectfully submit that this basis of rejection may be properly withdrawn.

The Examiner further contends that claims 7 and 8 are indefinite for allegedly reciting a use without any active, positive steps delimiting how the use is actually practiced. Applicants, without acquiescence, have canceled claims 7 and 8; thus, this basis of rejection is now moot and may be properly withdrawn.

Accordingly, Applicants respectfully submit that one having ordinary skill in the art would understand that the metes and bounds of the presently claimed invention are both clear and definite. Reconsideration and withdrawal of these bases for rejection is respectfully requested.

Claims Rejections Under 35 U.S.C. §101

Claims 7 and 8 stand rejected under 35 U.S.C. §101 as allegedly being directed to non-statutory subject matter. Specifically, the Examiner contends that claims 7 and 8 are drafted as "use" claims without setting forth any steps involved in the process, which results in an improper definition of a process and thus, is not statutory subject matter. Applicants respectfully disagree. However, Applicants, without acquiescence and solely in a good faith effort to expedite prosecution, have canceled claims 7 and 8; thus rendering this basis of rejection moot.

Claims Rejections Under 35 U.S.C. §112, First Paragraph, Enablement

Claims 1-3, 5, 7, and 9-10 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner contends that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully traverse this basis for rejection and submit that the as-filed specification fully enables the present claims. Moreover, one having ordinary skill in the art would be able to practice the entire breadth of the presently claimed invention without undue experimentation. Applicants, without acquiescence, have amended claim 10 to recite:

> "A method for the prevention and/or treatment of HIV infection in a patient, comprising administrating the compounds according to any one of claims 1-3 and the extract according to claim 4, thereby preventing and/or treating HIV infection in the patient."

Support for this amendment can be found throughout the as-filed specification, for example on pages 6-8 and thus, does not contain new matter.

The Examiner contends that the specification does not give any guidance as to the full range of conditions which could be treated or prevented using the instant claimed process. The Examiner further contends that in order to practice the claimed invention, one skilled in the art would have to speculate which conditions could be prevented using the claimed compounds found in the instant claims. Applicants respectfully disagree.

As noted above, the presently amended claims are directed to a method for the prevention and/or treatment of HIV infection. Applicants respectfully submit that the as-filed specification provides ample guidance with respect to practicing a method for the prevention and/or treatment of HIV infection. Such guidance includes, but is not limited to compounds, pharmaceutical formulations of said compounds, dosage forms, doses, and dosing schedules (see as-filed specification, pages 10-12, for example). The specific dosage for a given patient under specific conditions and for a specific disease will routinely vary, but determination of the optimum amount in each case can readily be accomplishes by simply routine procedures. *Ex Parte Skuballa,* 12 U.S.P.Q.2d 1570, 1571, 1989 WL 274384 (B.P.A.I. 1989). Applicants respectfully submit that in determining enablement "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt,* 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Citing Huff (J Med. Chem. 34(8) 1991, p. 2305-2314), the Examiner contends that the obstacles to therapeutic approaches and vaccine development with regard to retroviruses associated with AIDS in humans are well documented in the literature. The Examiner further contends that the existence of these obstacles establishes that the contemporary knowledge in the

art would prevent one of ordinary skill in the art from accepting any vaccine or immunization treatment or any therapeutic regimen on its face. Applicants respectfully disagree.

Applicants respectfully point out that the Examiner has mischaracterized the Huff reference, the skill in the art, and the problems encountered by those in the art at the time the instant application was filed. Applicants respectfully submit that Huff is merely a commentary on the strategies used to identify and create small molecules that inhibit HIV protease *circa* 1991. Moreover, the commentary in Huff is favorable with regard to the discovery and *in vitro* testing of HIV protease inhibitors and the promise they hold for *in vitro* treatment of HIV. Applicants respectfully submit that the *in vivo* effectiveness of HIV protease inhibitors has, in fact, been realized. For example, cocktails of HIV protease inhibitors marketed by various pharmaceutical companies are effective in the treatment of HIV infection.

Applicants respectfully submit that a search of the PubMed database at www.ncbi.nlm.nih.gov/Pubmed using the keywords "HIV", "protease", and "inhibitors" yielded only 152 articles, including 1 review article, when the publication date was limited to December 31, 1991. In stark contrast, the same search conducted for articles published up until October 22, 2003, which is the effective filing date of the subject application, yielded 7027 articles, including 911 review articles. One of skill in the art would clearly appreciate that much progress had been since the publication date of the Huff article and the state of the art at the time the instant application was filed, especially with regard to predictability, obstacles facing the skilled artisan, and the level of skill in the art.

The Examiner further contends that there is no established correlation between *in vitro* activity and accompanying treatment of viral infections, especially *in vivo*, and those skilled in the art would not accept allegations in the instant specification, or the *in vitro* date to be reliable predictors of success. In addition, the Examiner contends that there is no proof that the claimed compounds or compositions have ever been administered to a human or to an animal model. Applicants respectfully disagree.

Since the initial burden is on the Examiner to give reasons for the lack of enablement, the Examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not

required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985): [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

Applicants respectfully submit that the as-filed specification provides detailed *in vitro* working examples, wherein the presently claimed compounds are shown to have low cytotoxicity (see as-filed specification, Figure 1, for example) and display activity in blocking HIV cell fusion (see as-filed specification, Figure 3, for example) and inhibiting the cytopathic effect of HIV (see as-filed specification, Figure 5, for example). Moreover, the presently claimed compounds displayed comparable results to and fairly correlate to those of AZT and T-20, two well-known HIV therapeutics. Thus, based on results of the presently claimed compounds in the assays exemplified in the as-filed specification, Applicants respectfully submit that one having ordinary skill in the art would be able to practice the presently claimed method without undue experimentation.

Moreover, enablement of the claimed invention does not require a demonstration that the invention may be used therapeutically. Applicants submit that the Federal Circuit has clearly established that human clinical data sufficient to gain FDA approval is not required to establish patentability. In the landmark case of *In re Brana*, the Federal Circuit held that the FDA's requirements of testing for safety and effectiveness are not required by the patent laws. The Court stated, "[t]he Commissioner, as did the Board, confuses the requirement under the law for obtaining a patent with the requirements of obtaining government approval to market a particular drug for human consumption." 51 F.3d 1560, 1567 (Fed. Cir. 1995). The Court continued by stating that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Id. at 1568. Applicants also note that the rejection described in *In re Brana* was made under Section 112 and not under Section 101.

The Examiner's assertions, in part, appear to be that the specification does not enable the use of the claimed methods due to a lack of evidence regarding their human implementation. If this is true, the Action is asserting that the claimed invention lacks *in vivo* utility. Although this rejection is not made under 35 U.S.C. § 101, the legal standard to be applied is the same. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) (Although the Examiner rejected pharmaceutical compositions based on § 112, a § 101 rejection for lack of utility would also have been proper.) (See also "Legal Analysis Supporting Utility Examination Guidelines 60 F.R. 36263, July 14, 1995.)

Applicants respectfully submit that this rejection is improper in view of the PTO Guidelines. In no case has a Federal court required an applicant to support an asserted utility with data from human clinical trials. Moreover, in *In re Brana*, the Federal Circuit emphatically rejected the PTO position that human clinical testing is necessary to establish practical utility for an antitumor agent. 51 F.3d 1560. Importantly, the court noted, citing *In re Krimmel*, 130 U.S.P.Q. 205 (C.C.P.A. 1961):

> "We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, **even though it may eventually appear that the compound is without value in the treatment of humans**." (Emphasis added)

Here, the situation is analogous. The Applicants have demonstrated a method of preventing HIV infection in more than one *in vitro* human cell culture model; whether the method will eventually have commercial value in the treatment of humans is not a relevant inquiry to determine patentability.

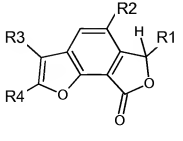
Applicants respectfully submit that in view of the as-filed disclosure, one having ordinary skill in the art would not encounter any undue experimentation in practicing the entire breadth of the presently claimed invention. Accordingly, Applicants submit that the as-filed specification fully enables the presently claimed invention. Reconsideration and withdrawal of this basis for rejection is respectfully requested.

Claims Rejections Under 35 U.S.C. §103(a)

Claims 1-6 and 9 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Padwa *et al.* (DN 138:170018 (2003); "Padwa") and/or Murray *et al.* (DN 106:101992 (1986); "Murray"). Specifically, the Examiner contends that Murray and Padwa teach benzofuranolactone compounds corresponding to those recited in the claims, and that structurally related compounds bearing similar substituents, such as propyl instead of ethyl, would have been obvious to one having ordinary skill in the art as the results would not have been unexpected. The Examiner further contends that claim 6 would have been an obvious method as it is well-known in the art of plant extracts to separate an isolate plant compounds in the manner recited in the claims.

Applicants respectfully traverse these bases for rejection and submit that the Action fails to establish a *prima facie* case of obviousness against the presently claimed invention. The Action fails to provide a sufficient basis for one having ordinary skill in the art to predictably arrive at the presently claimed invention with any reasonable expectation of success.

In the instant case, the Action has not provided sufficient rationale to support why the prior art would have led the skilled artisan to modify the prior art compounds identified by the Examiner and arrive at the presently claimed concentricolides with any reasonable expectation of success. Particularly, the Action has failed to provided a sufficient rationale that would lead one having ordinary skill in the art to modify the furan rings in either compound RN 289673-95-6 or RN 106895-67-4 to 2,3 dihyrofuran (*i.e.*, the carbon-carbon double bond between the ring carbons attached to the R3 and R4 groups).



Furthermore, the Action has failed to provide a sufficient rationale that would lead the skilled artisan to modify the furanone ring of RN 289673-95-6 by adding a C1-C4 alkyl group at position R1 as presently claimed.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492. F.3d 1350 (Fed. Cir. 2007), the Court noted that "In addition to structural similarity between the compounds, a *prima facie* case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985)." Furthermore, the Court pointed to *In re Deuel,* 51 F.3d 1552, 1558 (Fed. Cir. 1995), where the Court stated that "[n]ormally a *prima facie* case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.*

The Court clarified, however, that in order to find a *prima facie* case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones,* 958 F.2d 347 (Fed. Cir. 1992); *Dillon*, 919 F.2d 688; *Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984)).

The *Takeda* Court concluded that test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*. While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry.

Id. Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.

Applicants respectfully submit that the Action has clearly failed to provide a sufficient basis of rationale that would lead the skilled artisan to modify the prior art compounds to arrive at the presently claimed concentricolides. Thus, Action has failed to establish a *prima facie* case of obviousness against the presently claimed compounds because one having ordinary skill in the art would not have modified the compounds of Murray and Padwa to predictably arrive at the presently claimed invention

The Examiner further contends that claim 6 would have been an obvious method as it is allegedly well-known in the art of plants extract to separate and isolate plant compounds in the manner recited in the claims. Applicants respectfully disagree.

Applicants respectfully submit that the Action has failed to provide any evidence, either in the form of prior art references and/or sufficient rationale, that one having skill in the art would be able to carry out an extraction of the fruiting bodies of *Daldinia* as claimed and isolate the presently claimed compounds of Formula II. The Action has merely offered a conclusory statement that the skilled artisan would find the presently claimed method of claim 6 obvious because it was allegedly well-known in the art.

Applicants respectfully submit that the *KSR* Court noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S. at ___, 82 USPQ2d at 1396.

At a minimum, it must be demonstrated that the cited references provide a sufficient basis to predictably arrive at the presently claimed invention, and even assuming, *arguendo*, that the cited references teach each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. See *KSR v. Teleflex, Inc.,* No. 04-1350 at 4, 14 (U.S. Apr. 30,

2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art").

Applicants respectfully submit that the Action has failed to identify any prior art describing or suggesting a method of making extracts from the fruiting bodies of *Daldinia* that would allow the skilled artisan to predictably isolate the presently claimed compounds of Formula II with any reasonable expectation of success. Thus, the Action has failed to establish a *prima facie* case of obviousness against the presently claimed method of claim 6.

Accordingly, as the Action fails to establish a prima facie case of obviousness against the presently claimed invention, Applicants respectfully request reconsideration and withdrawal of these bases for rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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